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Ethanol preexposure attenuates the interaction of ethanol and cocaine in taste aversion learning

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Abstract

Although the potentiating effects of ethanol and cocaine have been well documented, little has been reported regarding the effects of ethanol or cocaine history on this interaction. In the present study, female Long–Evans rats received five exposures to ethanol (3.5 g/kg ip) or vehicle prior to taste aversion conditioning in which a novel saccharin solution was paired with either ethanol (0.56 g/kg ip), cocaine (25 mg/kg sc) or the combination (or the drugs' vehicle) for a total of five conditioning trials. Nonpreexposed subjects conditioned with the ethanol/cocaine combination displayed aversions, drinking levels significantly less than nonpreexposed subjects conditioned with either drug alone. Further, the aversions produced by the combination were greater than the sum of the aversions produced by ethanol and cocaine, alone. Ethanol-preexposed animals conditioned with the combination displayed an attenuated aversion, drinking significantly greater amounts of saccharin than nonpreexposed conditioned subjects and not differing from controls. Although the basis for the attenuation by ethanol of the aversions induced by the drug combination is not known, the present findings may have implications for the use and abuse of the combination in that alcohol history may reduce the subsequent toxicity of the combination that in turn may affect its acceptability.

Keywords: Ethanol; Cocaine; UCS preexposure; Conditioned taste aversion; Rats

1. Introduction

The interaction of ethanol and cocaine has been widely demonstrated for a variety of behavioral and physiological effects, including liver (Boyer and Petersen, 1990) and cardiovascular (Foltin and Fischman, 1989; Perez-Reyes and Jeffcoat, 1992) toxicity, depression of myocardial function (Henning et al., 1994; Uszenski et al., 1992), postnatal mortality (Church et al., 1991), delayed offspring physical maturation (Church et al., 1991), disruption of rotarod performance (Masur et al., 1989; Misra et al., 1989; Rech et al., 1978) and suppression of schedule-controlled responding (Sobel and Riley, 1997). Although the interaction is often reported and occurs under a variety of parametric conditions and within a number of procedures (see above), its basis remains unknown.

Given that the interaction between ethanol and cocaine is well documented, it is interesting that very little has been examined on the effects of ethanol or cocaine history on this interaction (Hedaya and Pan, 1996; Peris et al., 1997). In one of the initial assessment of such exposure, Peris et al. (1997) examined the effects of chronic exposure (13–20 days) to ethanol on disruption in locomotor coordination subsequently induced by a cocaine and ethanol combination. Rats pretreated with saline and given ethanol plus cocaine showed disruption in performance. Conversely, rats pretreated with ethanol prior to the combination exhibited very little disruption of behavior, suggesting that ethanol preexposure attenuated the disruptive effect of the combination. The fact that little has been reported on the effects of ethanol (or cocaine) history on their interaction is surprising given the reports that ethanol and cocaine use alone antedates the use of the combination of ethanol and cocaine as well as a variety of other combinations of psychoactive drugs (Carroll et al., 1993; Helzer and Pryzbeck, 1988; Kandel, 1975; Martin et al., 1996; Rounsaville et al., 1982, 1987; Schuckit, 1985) and that exposure to ethanol (or cocaine) has been reported to impact subsequent sensitivity to cocaine (or ethanol) (Itzhak and Martin, 1999; Kunin et al., 1999; Manley and Little, 1997; Peris et al., 1997; York and MacKinnon, 1999).

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Although ethanol preexposure has been reported to affect the subsequent motoric reactivity to the combination of ethanol and cocaine (see above), as noted, ethanol and cocaine in combination produce a variety of physiological and behavioral effects greater than either alone. Accordingly, it is important to examine the generality of such exposure effects and the conditions under which such effects occur. The present experiment extended this analysis by assessing the effects of ethanol preexposure on the interaction of ethanol and cocaine within the conditioned taste aversion (CTA) preparation in which aversions induced by the combination are not only greater than aversions to either drug alone, but also greater than the summation of aversions induced by the two individual compounds (see Etkind et al., 1998). This response system is of interest in that a drug's acceptability (in terms of its self-administration) appears to be a function of the balance between its rewarding and aversive effects (Cunningham and Henderson, 2000; Gaiardi et al., 1991; Gauvin et al., 2000; Stefurak et al., 1990; Stolerman and D'Mello, 1981; White et al., 1977; Wise et al., 1976). That is, if the drug's aversive effects outweigh its rewarding effects, the drug is not likely to be self-administered. A change in either of these affective responses, therefore, could affect the drug's subsequent acceptability and use, e.g., if the aversive effects of the drug weaken, its use may increase (due to an overall increase in its perceived rewarding effects) (see Ettenberg et al., 1982; Lynch and Carroll, 2001; Pizzi and Cook, 1996; for an alternative interpretation of the nature of aversion learning, see Grigson, 1997).

One procedure reported to affect the aversive and rewarding properties of a drug (or a drug combination) is drug preexposure. For example, the ability of a drug to induce a taste aversion, an index of the drug's aversiveness or toxicity (see Riley and Tuck, 1985), decreases with drug preexposure (for review, see Riley and Simpson, 2001; although see Bienkowski et al., 1998c; Heinrichs et al., 1998; Lipinski et al., 1995). Conversely, the ability of a drug to condition a place preference, an index of the drug's reinforcing effects, has been reported to increase with preexposure (Gaiardi et al., 1991; Le Pen et al., 1998; Lett, 1989; Shippenberg and Heidbreder, 1995). Whether these changes reflect independent processes (e.g., habituation to the drug's aversive effects or sensitization to its reinforcing effects) or co-occurring and interacting processes is not clear. What is clear, however, is that the affective properties of drugs as measured in these preparations change with prior exposure to the drug.

To assess the effects of ethanol preexposure on aversions induced by the combination, rats were given five exposures to ethanol (3.5 g/kg) prior to receiving exposure to a novel solution paired with injections of either ethanol (0.56 g/kg), cocaine (25 mg/kg) or the combination of both drugs. The effects of ethanol preexposure in these subjects were compared with those in similarly treated subjects preexposed to the ethanol vehicle, i.e., distilled water.

2. Method

2.1. Subjects

The subjects were 68 experimentally naive, female rats of Long–Evans descent, approximately 120 days of age and between 180 and 250 g in weight at the beginning of the experiment. Guidelines established by the Institutional Animal Care and Use Committee at American University were followed at all times.

2.2. Apparatus

Subjects were individually housed in stainless-steel, wire-mesh cages on the front of which graduated Nalgene tubes were placed to provide 20-min access to water or saccharin. Subjects were maintained on a 12L:12D cycle (lights on at 0800 h) and at an ambient temperature of 23 °C for the duration of the experiment. Food was available ad libitum.

2.3. Drugs and solutions

Cocaine hydrochloride (generously provided by NIDA) was prepared as a 10-mg/ml solution in distilled water. Ethanol (generously provided by the Department of Chemistry, American University) was prepared as a 95% solution in distilled water and was diluted to a 15% injectable solution. Saccharin (0.1% sodium saccharin, Sigma) was prepared as a 1 g/l solution in tap water.

2.4. Procedure

2.4.1. Phase I: Habituation

Prior to water deprivation, animals were adapted to the housing environment with food and water available ad libitum for approximately 20 days. Following 23 h water deprivation, subjects were given 20-min access to water for 12 consecutive days until they approached and drank from the tube within 2 s of its presentation.

2.4.2. Phase II: Preexposure

On Day 1 of Phase II, subjects were given 20-min access to water. Following this exposure, subjects were ranked according to their water consumption and were assigned to one of two preexposure groups, Groups E and W, such that mean water consumption was similar for the two groups. Four to five hours following water consumption, subjects in Group E were given a 3.5 g/kg intraperitoneal injection of ethanol (Kulkosky et al., 1980), while subjects in Group W were given an equivolume intraperitoneal injection of distilled water. These preexposure injections were given every fourth day for a total of five drug exposures. Subjects received 20-min access to water on the intervening recovery days. No injections were given following water access on these days. The specific parameters of preexposure were based on other work from this laboratory assessing the

effects of drug preexposure on the acquisition of CTAs (Riley and Diamond, 1998; Riley and Simpson, 1999; see Riley and Simpson, 2001 for a review of the drug preexposure effect in aversion learning).

2.4.3. Phase III: Conditioning

On Day 1 of this phase, all subjects were given 20-min access to a novel saccharin solution. Based on their baseline saccharin consumption, subjects were then given either an intraperitoneal injection of 0.56 g/kg ethanol, a subcutaneous injection of 25 mg/kg cocaine, injections of both drugs or injections of the drugs' vehicles immediately after saccharin consumption. This resulted in eight groups: W/E, W/C, W/E + C, W/W, E/E, E/C, E/E + C and E/W. The first letter in each group designation refers to the compound given during preexposure, i.e., water (W) or ethanol (E). The second letter refers to the compound(s) given during conditioning, i.e., ethanol (E), cocaine (C), the ethanol/cocaine combination (E + C) or water (W). All subjects injected with ethanol, cocaine or water during this phase received two injections (i.e., the first injection was drug and the second injection was vehicle) on each conditioning trial to match the number of injections given to the subjects injected with both ethanol and cocaine (i.e., Groups E/E + C and W/E + C). On the following three water-recovery days, all subjects were given 20-min access to water. No injections were given following water access on these days. This alternating procedure of conditioning/water recovery was repeated until all subjects received five complete cycles. On the day following the final water-recovery session, all subjects were given 20-min access to saccharin in a final one-bottle test of the aversion to saccharin. No injections were given following this test. The specific parameters of conditioning were those of Etkind et al. (1998) who reported that ethanol (0.56 g/kg ip) and cocaine (25 mg/kg sc) alone produced weak (or no) aversions, but whose combination resulted in marked suppression of consumption. Thus, these parameters provided a baseline to assess the effects of ethanol preexposure.

2.5. Statistical analysis

Differences in mean water consumption during the preexposure phase were assessed using a 2×5 repeated-measures analysis of variance (ANOVA) with between-subjects variable of Preexposure drug (ethanol or vehicle) and within-subjects variable of Preexposure day (1–5). Post hoc assessments were conducted using independent sample *t* tests. Within-subjects differences in consumption over preexposure (as indexed by differences in consumption from baseline, i.e., Preexposure Day 1) were assessed using paired sample *t* tests (Bonferroni correction). Alpha was set at .05.

Differences in mean saccharin consumption during conditioning for each group were assessed using a $2 \times 4 \times 5$ repeated-measures ANOVA with between-subjects variables of Preexposure drug (ethanol or vehicle) and Conditioning Drug (ethanol, cocaine, ethanol/cocaine and vehicle) and within-subjects variable of Trial (1–5). Post-hoc assessments were conducted using Tukey HSD pairwise comparisons. Within-subjects differences in consumption from baseline (Trial 1) were assessed using paired sample *t* tests (Bonferroni correction). Alpha was set at .05.

3. Results

3.1. Preexposure

Fig. 1 illustrates the mean (±S.E.M.) consumption of water for subjects receiving distilled water (Group W) and ethanol (Group E) over repeated preexposures. A 2×5 re peated-measure ANOVA revealed a significant Preexposure Day effect [$F(4,264) = 46.857$; $P < .001$], a significant Preexposure Day × Preexposure Drug interaction [$F(4,264) = 7.132$; $P < .05$], but no significant Preexposure Drug effect [$F(1,66) = 0.200$; $P > .05$]. Within-subjects paired sample *t* tests (Bonferroni corrected $P = .0125$) revealed that relative to the baseline (Preexposure Day 1), water consumption for both groups significantly decreased on Trials 2–5 ($t \geq 3.468$; $df = 33$; P's $\leq .001$). Although there was a significant Preexposure Day × Preexposure Drug interaction, post hoc assessments using independent sample *t* tests revealed that at no point during preexposure did Groups E and W differ ($t \geq 1.090$; $df = 66$; P's $> .001$). However, paired sample *t* tests revealed that there was an increase in consumption from Trial 4 to Trial 5 for Group E ($t = 5.054$; $df = 33$; $P < .001$), whereas there was no such increase for Group W ($t = 0.569$; $df = 33$; $P > .05$).

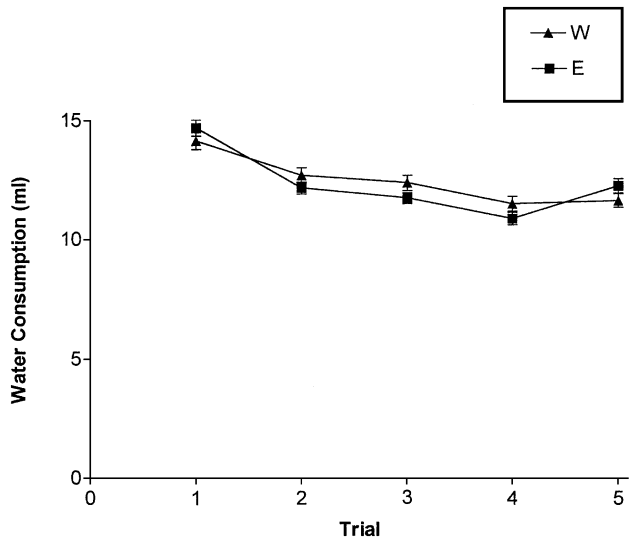

Fig. 1. The mean (±S.E.M.) water consumption of subjects receiving injections of ethanol (Group E) or distilled water (Group W) over repeated preexposures. All preexposures were given intraperitoneally, every fourth day.

3.2. Conditioning

3.2.1. Water-preexposed subjects

Fig. 2 illustrates the mean (±S.E.M.) consumption of saccharin for water-preexposed (top panel) and ethanol-preexposed (bottom panel) groups over repeated conditioning trials. A 2 × 4 × 5 repeated-measures ANOVA revealed significant effects of Trial [$F(4,240) = 25.662$; $P < .001$], Preexposure Drug [$F(1,60) = 14.648$; $P < .001$] and Conditioning Drug [$F(3,60) = 8.70$; $P < .001$] and significant Preexposure Drug × Conditioning Drug [$F(3,60) = 7.100$; $P < .001$], Preexposure Drug × Trial [$F(4,240) = 15.326$; $P < .001$], Conditioning Drug × Trial [$F(12,240) = 6.066$; $P < .001$] and Preexposure Drug × Conditioning Drug × Trial interactions [$F(12,240) = 2.982$; $P < .001$]. Post-hoc assessments using Tukey HSD yielded the following results. On the initial conditioning trial, there were no significant differences among water-preexposed subjects (all P's $\geq .151$), with all groups drinking approximately 9.5 ml of saccharin (see Fig. 2; top panel). Over subsequent conditioning trials, significant differences emerged among groups. Specifically, subjects preexposed to water and injected with ethanol during conditioning (Group W/E) never differed significantly from subjects preexposed to water and given vehicle injections during conditioning, i.e., Group W/W (all P's $\geq .378$). On the other hand, subjects preexposed to water and given cocaine during conditioning (Group W/C) drank significantly less saccharin than subjects in Group W/W on Trials 3 and 5 (P's $\leq .020$). Subjects preexposed to water and given the ethanol and cocaine combination during conditioning (Group W/E + C) also drank significantly less saccharin than Group W/W, in this case on Trials 3–5 (P's = .001). Further, subjects in Group W/E + C drank significantly less than Group W/E on Trials 3, 4 and 5 (P's $\leq .038$) and Group W/C on Trials 4 and 5, respectively (P's $\leq .003$).

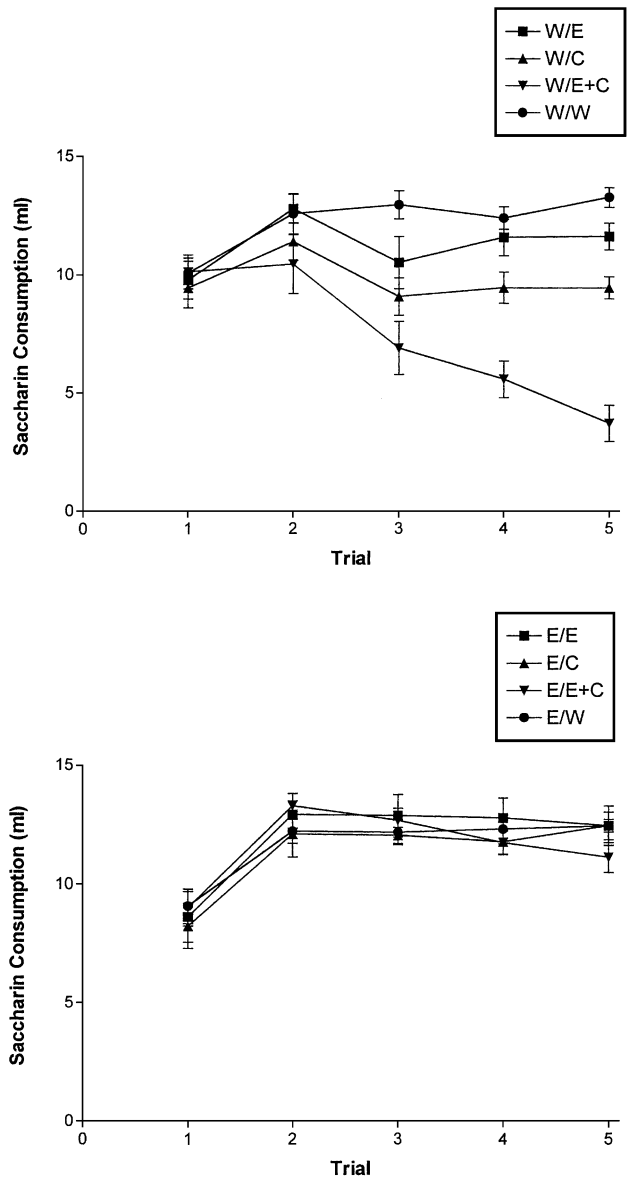

Fig. 2. The mean (±S.E.M.) saccharin consumption of water preexposed (Groups W/E, W/C, W/E + C, W/W; top panel) and ethanol-preexposed (Groups E/E, E/C, E/E + C, E/W; bottom panel) subjects over repeated conditioning trials. The first letter in the group designation refers to the drug received during preexposure, i.e., distilled water (W) or ethanol (E); the second letter refers to the drug given during conditioning, i.e., distilled water (W), ethanol (E), cocaine (C) or the ethanol/cocaine combination (E + C).

Within-subjects paired sample t tests (Bonferroni corrected $P = .0125$) yielded the following results. Specifically, subjects in Group W/W increased saccharin consumption over trials, drinking significantly more on Trial 5 than on Trial 1 ($t = 4.432$; $df = 7$; $P = .003$). Subjects preexposed to water and conditioned with either ethanol or cocaine (Groups W/E and W/C) displayed no significant changes in saccharin over conditioning ($t = 2.729$; $df = 8$; $P \geq .026$ for Group W/E; $t \leq 2.539$; $df = 8$; $p \geq .035$ for Group W/C). On the other hand, subjects preexposed to water and conditioned with the combination (Group W/E + C) significantly decreased saccharin consumption over conditioning, drinking significantly less saccharin on Trials 3–5 than on Trial 1 (t's ≥ 3.567; $df = 7$; P's $\leq .009$).

3.2.2. Ethanol-preexposed subjects

On the initial conditioning trial, there were no significant differences among ethanol-preexposed subjects (all P's $\geq .996$), with all groups drinking approximately 9.5 ml of saccharin (see Fig. 2; bottom panel) The pattern of consumption for all four groups was similar for the remainder of conditioning, again with no significant differences among groups (all P's $\geq .756$), i.e., there was no evidence of the acquisition of aversions in any ethanol-preexposed group. Consistent with these between-subjects comparisons, within-subject analysis revealed that subjects in all ethanol-preexposed groups significantly increased consumption over conditioning (all P's $\leq .012$, although see Trials 4 and 5 for Group E/W and Trial 5 for Group E/E + C).

Comparisons of water- and ethanol-preexposed groups revealed that subjects preexposed to ethanol and given the

ethanol and cocaine combination during conditioning drank significantly more saccharin than water-preexposed subjects given the combination (see Trial 3, 4 and 5; all P's = .001). Further, subjects in Group E/C drank significantly more than subjects in Group W/C on Trial 5 (P = .013). Thus, ethanol preexposure attenuated the acquisition of aversions in Groups E/E + C and E/C. There was no effect of ethanol preexposure in Groups E/W and E/E, i.e., Groups E/W and W/W and Groups E/E and W/E did not differ at any point during conditioning (all P's $\geq$ .395).

4. Discussion

Although the interaction between ethanol and cocaine is well documented, investigations into the effects of ethanol history on the interaction are limited (see above). In order to extend the scope of research on such drug exposure, the present experiment examined the effects of ethanol history on the interaction of ethanol and cocaine within CTA learning. Such an assessment may be important in relation to the possible abuse potential of the combination of ethanol and cocaine given the position that a drug's (or drug combination's) acceptability is a function of the balance between its reinforcing and aversive effects and that this balance can be affected by changes in either of these two affective states (see Cunningham and Henderson, 2000; Gaiardi et al., 1991; Gauvin et al., 2000; Stefurak et al., 1990; Stolerman and D'Mello, 1981).

As noted, in vehicle-preexposed animals, the ethanol and cocaine combination produced a greater aversion than that produced by cocaine or ethanol alone. Further, the aversions produced by the combination were greater than the sum of the aversions produced by ethanol and cocaine, alone. For example, on Trial 4, the percent shift in saccharin consumption from nonconditioned controls for the vehicle-preexposed group conditioned with the ethanol/cocaine combination was approximately 55%. The sum of the percent shift for the vehicle-preexposed subjects conditioned with ethanol and cocaine, alone, was 31% (7% and 24% following ethanol and cocaine, respectively). Similarly, on Trial 5, the percent shift following the combination was 72%, whereas the summed value following ethanol and cocaine, alone, was 41% (ethanol—12% and cocaine—29%). This effect of the combination is similar to that noted by Etkind et al. (1998) who reported the synergistic interaction of ethanol and cocaine in taste aversion learning. Interestingly, in animals preexposed to ethanol, the combination of ethanol and cocaine failed to produce significant aversions. In fact, consumption in the ethanol-preexposed subjects conditioned with the combination did not differ from controls and was significantly greater than that in subjects preexposed to water and given the ethanol/cocaine combination during conditioning. Thus, preexposure to ethanol attenuated the effects of the ethanol/cocaine combination in aversion learning, an attenuating effect of ethanol preexposure similar to that reported within other preparations, e.g., locomotor behavior (see Peris et al., 1997). It remains to be determined if the effects of ethanol history on the interaction between ethanol and cocaine are modulated by the specific parameters of drug exposure or if the effects reported here generalize to other drug histories, e.g., cocaine prior to the ethanol/cocaine combination.

Although the basis for the attenuating effects of ethanol on aversions induced by the combination is not known, the effects in the present experiment parallel those of other work assessing the effects of ethanol preexposure on aversion learning. Specifically, preexposure to ethanol has been reported to attenuate aversions induced by ethanol as well as a variety of other compounds, including cocaine (for a review, see Riley and Simpson, 2001). In relation to the effects of ethanol preexposure on ethanol-induced aversions, as early as 1974, Berman and Cannon reported that preexposure to ethanol fully attenuated ethanol-induced aversions with the degree of attenuation a direct function of the dose and number of exposures of ethanol given during preexposure (see also Cannon et al., 1975; De Beun et al., 1996a,b; Stewart et al., 1991). More recently, our laboratory (Grakalic and Riley, 1999; 2000) and others (Kunin et al., 1999) have reported that preexposure to ethanol attenuated aversions induced by cocaine. For example, Grakalic and Riley (2000) demonstrated that animals preexposed to 3.5 g/kg ethanol and conditioned with 25 mg/kg cocaine displayed attenuated cocaine-induced aversions, drinking levels significantly greater than nonpreexposed, conditioned subjects throughout conditioning. As above, the attenuating effect of ethanol on cocaine aversions is also affected by the dose of ethanol given during preexposure (see Grakalic and Riley, unpublished data). Although the mechanism underlying the attenuating effects of ethanol on aversions induced by ethanol and by cocaine has not been determined, it has been generally suggested that drug preexposure weakens the aversive effects of the conditioning compound, possibly through nonassociative processes such as (cross) tolerance, adaptation and habituation, or through associative mechanisms such as blocking or compensatory conditioning (see Riley and Simpson, 2001; for an alternative interpretation of the effects of drug preexposure on aversion learning which focused not on adaptation to the aversive effects of the drug, but instead on sensitization to its rewarding effects, see Gaiardi et al., 1991; 1997).

That ethanol affects aversion learning to individual compounds such as ethanol and cocaine may be important to the present findings. That is, the failure of ethanol-preexposed subjects to display aversions to saccharin subsequently paired with the ethanol/cocaine combination may be a function of the attenuating effects of ethanol on the aversive effects of ethanol and/or cocaine. Although ethanol has been widely reported to attenuate ethanol-induced taste aversions (see Barker and John, 1978; Berman and Cannon, 1974; Bienkowski et al., 1998a,b; Cannon et al., 1975, 1977; De Beun et al., 1996a,b; Hunt and Rabin, 1988; June et al., 1992;

Rabin et al., 1988; Risinger and Cunningham, 1995; Stewart et al., 1991), the effects of ethanol preexposure on aversions induced by ethanol could not be assessed in the present experiment, primarily because the dose of ethanol (0.56 g/kg) used in conditioning did not induce aversions on its own (see Etkind et al., 1998). On the other hand, cocaine did induce aversions and subjects preexposed to ethanol and conditioned with cocaine displayed no evidence of cocaine-induced taste aversions relative to nonconditioned controls (whether vehicle or ethanol preexposed) and drank significantly more than cocaine-conditioned subjects that had been preexposed to vehicle (see Trial 5). Thus, ethanol preexposure attenuated aversions induced by cocaine, an effect consistent with previous reports by Kunin et al. (1999) and Grakalic and Riley (1999, 2000).

Although ethanol's effects on the aversions induced by the combination could be a function of its effects on each of the two elements of the compound, it is likely that other factors are involved as well. This conclusion is based on the fact that the aversions induced by the combination were greater than the sum of the aversions produced by ethanol and cocaine alone. That is, ethanol and cocaine must have interacted in some manner other than simple effect additivity to produce the aversions reported in the present work. Several sources for this interaction are possible, and each could be affected by ethanol preexposure. For example, it has recently been reported that the unique cocaine metabolite, cocaethylene, which is produced only in the presence of ethanol, has a myriad of effects similar to those of cocaine and has been reported to be responsible under some preparations for the greater effects of the combination of cocaine and ethanol (Boyer and Petersen, 1990; Bunney et al., 2001; Etkind et al., 1998; Farre et al., 1993; Foltin and Fischman, 1989; Masur et al., 1989; Misra et al., 1989; Moolten and Kornetsky, 1990). That is, cocaethylene's effects summate with those of cocaine (and ethanol) to produce an effect greater than that of cocaine or ethanol or an effect greater than their summed effects. If cocaethylene was involved in the ability of the ethanol/cocaine combination to induce significantly greater taste aversions (see Etkind et al., 1998; present results), it is possible that ethanol preexposure affected the ability of cocaethylene to induce aversions, thereby reducing the overall effect of the drug combination. Although possible, we have previously reported that cocaethylene is only marginally aversive in the taste aversion design and that the doses at which aversive effects are reported (i.e., 50 mg/kg) far exceed the dose produced by the combination of cocaine (25 mg/kg) and ethanol (0.56 g/kg) (for a discussion, see Etkind et al., 1998). However, the effects of ethanol preexposure on cocaethylene-induced aversions have not been directly tested, so it remains unknown to what degree such aversions would be affected by ethanol preexposure and to what extent such attenuation (if any) would contribute to the effects of ethanol on the combination.

Cocaine and ethanol could be interacting in ways other than the summation of behavioral effects or the production of unique metabolites. Specifically, the two compounds could be affecting each other's pharmacokinetic properties which in turn could be impacting the duration or dose of either compound. These changes could be mediating the greater aversions induced by the compound. For example, studies have demonstrated that when ethanol and cocaine are administered concurrently, ethanol increases peak plasma concentrations and plasma levels of cocaine (Dean et al., 1992; Farre et al., 1993; McCance-Katz et al., 1998; Perez-Reyes and Jeffcoat, 1992; Vadlamani et al., 1984). Similarly, Farre et al., (1993) reported that in humans, ethanol increased cocaine's plasma levels and concentrations in the liver (see also, Perez-Reyes and Jeffcoat, 1992). These changes in cocaine pharmacokinetics caused by ethanol are not limited to humans only. For example, Dean et al. (1992) demonstrated that ethanol pretreatment 30 min prior to cocaine injections increased cocaine concentration in the liver of male Wistar rats. Accordingly, preexposure to ethanol could affect the ability of either compound to modulate each other's clearance and/or distribution that might in turn affect their ability to affect their pharmacokinetics. Although it is possible that such interactions mediate the increased aversion with the combination and that these pharmacokinetic interactions are affected by ethanol preexposure, until blood levels of cocaine and ethanol are assessed in naïve and ethanol-exposed subjects, such possibilities remain speculative.

Independent of the mechanism, the present study may have implications for the co-use and abuse of the combination. The basis for this suggestion stems from the fact that many recreational drugs (including ethanol and cocaine) have dual properties. That is, they can be both reinforcing and aversive (Goudie, 1979; Grigson, 1997; Hunt and Amit, 1987). In relation to their reinforcing effects, both cocaine and ethanol have been reported to be self-administered (Hunt and Amit, 1987; Moolten and Kornetsky, 1990), to condition place preferences (Gauvin and Holloway, 1991) and to lower the threshold for electrical brain stimulation (Moolten and Kornetsky, 1990). In relation to their aversive effects, both cocaine and ethanol have been reported to produce dose-dependent CTAs (Ferrari et al., 1991; Kulkosky et al., 1980). Interestingly, such effects have been produced with some psychoactive compounds within the same preparation (White et al., 1977; Wise et al., 1976). For example, Wise et al. (1976) demonstrated that rats learned to press a lever for the self-administration of amphetamine or apomorphine, but avoided the taste of saccharin that was associated with the self-administered drugs. Thus, both amphetamine and apomorphine seem to have aversive and rewarding properties that occur concurrently (see also Stefurak et al., 1990).

These dual properties of drugs may have implications for their use and abuse. Specifically, the likelihood of the use of a drug may depend on the relative strengths of its aversive and rewarding effects. That is, if the rewarding effects of a drug are greater than its aversive effects, the likelihood of its subsequent use may be increased. Conversely, if the aver-

sive effects are greater than its rewarding effects, the likelihood of its subsequent use may decrease (Ettenberg et al., 1982; Goudie, 1979). In this context, if a drug's acceptability is dependent on these two properties, it might be expected that any manipulation affecting these properties might also affect their use (see Gaiardi et al., 1997; Riley and Simpson, 2001). Support for this position has been presented in a variety of studies (see Badia-Elder and Kiefer, 1999; Kiefer et al., 1994; Stewart et al., 1991) examining the effects of ethanol preexposure on the subsequent aversive and rewarding effects of ethanol. Specifically, it has been reported that ethanol preexposure not only attenuated ethanol's aversive effects, but it also increased its rewarding effects, suggesting that with chronic exposure the rewarding and/or aversive properties of ethanol changed (see also Risinger and Cunningham, 1995).

In this context of the reinforcing and aversive effects of various compounds, it is important to note that similar dual properties have been reported with the combination of ethanol and cocaine (Farre et al., 1993; Grant and Harford, 1990; Lewis and June, 1994; McCance-Katz et al., 1998; Perez-Reyes and Jeffcoat, 1992). For example, Lewis and June (1994) demonstrated that low doses of cocaine and ethanol given concurrently produced a decrease in brain stimulation reward threshold and an increase in response rate, suggesting that cocaine and ethanol may share a common neural mechanism related to reward. Further, McCance-Katz et al. (1998) indicated that the co-use of cocaine and ethanol produced greater euphoria and increased perception of well-being than that usually associated with cocaine. Conversely, others have reported that the combination of ethanol and cocaine is more aversive than either drug alone (e.g., Etkind et al., 1998; Sobel and Riley, 1997), an effect consistent with other toxicological effects (e.g., increased liver and cardiovascular toxicity, a greater depression in myocardial function, increased teratological effects, a greater decrease in birth weights and increased postnatal mortality). As suggested in the present experiment, if preexposure to ethanol can result in the reduction of the aversiveness of the combination of ethanol and cocaine (as indicated by a weak CTA), an ethanol history may make the combination of ethanol and cocaine more acceptable. Accordingly, such a history may increase the likelihood of its use.

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